BMJ open

Passive smoking at home is a risk factor for community-acquired pneumonia in older adults

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-005133
Article Type:	Research
Date Submitted by the Author:	25-Feb-2014
Complete List of Authors:	Almirall, Jordi; Hospital de Mataro, Intensive Care Unit Serra-Prat, Mateu; Hospital de Mataró, Research Unit Bolibar, Ignasi; IIB Sant Pau, Clinical Epidemiology and Public Health, Institut de Recerca Biomedica Palomera, Elisabet; Consorci Sanitari del Maresme, Unitat de Recerca Roig, Jordi; Hospital Nostra Senyora de Meritxell, Pneumologia Hospital, Imma; 5Institut Català de la Salut (ICS),, ABS Valls Carandell, Eugenia; IB-SALUT Balears, Agustí, Mercè; Institut Català de la Salut (ICS), ABS Targue Ayuso, Pilar; INSALUD, Valencia, Estela, Andreu; IB-SALUT Balears, Torres, Antoni; Hospital Clinic i Provincial, Pneumology
Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Epidemiology, Public health
Keywords:	EPIDEMIOLOGY, Public health < INFECTIOUS DISEASES, Infection control < INFECTIOUS DISEASES, Thoracic medicine < INTERNAL MEDICINE

Passive smoking at home is a risk factor for community-acquired pneumonia in older adults

Jordi Almirall[1], Mateu Serra-Prat[2], Ignasi Bolíbar[3], Elisabet Palomera[2], Jordi Roig[4], Imma Hospital[5], Eugenia Carandell[6], Mercè Agustí[5], Pilar Ayuso[7], Andreu Estela[6], Antoni Torres[8] and the Study Group of Community-Acquired Pneumonia in Catalan Countries (PACAP)

[1]Critical Care Unit, Hospital de Mataró, Universitat Autònoma de Barcelona, Ciber Enfermedades Respiratorias, CIBERES, Barcelona, Spain.

[2]Research Unit, Hospital de Mataró. CIBEREHD, Barcelona, Spain.

[3]Department of Clinical Epidemiology and Public Health, Institut de Recerca Biomedica (IIB Sant Pau) Barcelona, Universitat Autònoma de Barcelona, CIBERESP, Barcelona, Spain.

[4]Hospital Nostra Senyora de Meritxell, Principat d'Andorra.

[5]Institut Català de la Salut (ICS), Barcelona, Spain.

[6]IB-SALUT Balears, Palma de Mallorca, Spain.

[7]INSALUD, Valencia, Spain.

[8]Service of Pneumology, Institut Clínic del Torax, IDIBAPS, Hospital Clínic de Barcelona. Universitat de Barcelona, CIBERES, Barcelona, Spain.

J. Almirall, e-mail: jalmirall@csdm.cat
M. Serra-Prat, e-mail: mserra@csdm.cat
I. Bolíbar, e-mail: ibolibar@santpau.es
E. Palomera, e-mail: epalomera@csdm.cat
J. Roig, e-mail: averoig@mypic.ad
I. Hospital, e-mail: ihospitalg.tarte.ics@gencat.cat
E. Carandell, e-mail: ecarandell@ibsalut.caib.es
M. Agustí, e-mail: magustip@telefonica.net
P. Ayuso, e-mail: payuso77@hotmail.com
A. Estela, e-mail: andreu.estela@ssib.es
A. Torres, e-mail: atorres@clinic.ub.es

Correspondence to: Dr. Jordi Almirall, Intensive Care Unit, Hospital de Mataró, Carretera de Cirera s/n, E-08304 Mataró, Barcelona, Spain. Telephone number +34 93 7417700, fax +34 93 7417770, e-mail: jalmirall@csdm.cat

Keywords: Community-acquired pneumonia, passive smoking, older adults.

Word count: 1963.

Key messages

- What is the key question?
Is passive smoking exposure at home a risk factor for community-acquired pneumonia in adults?
- What is the bottom line?
Passive smoking at home might be a risk factor for CAP in older adults (65 years or more).
- Why read on?
The effect of passive smoking on CAP in adults is controversial, and the present population-based study adds new evidence on this topic.

Abstract

Background To assess whether passive smoking exposure at home is a risk factor for community-acquired pneumonia (CAP) in adults.

Methods A population-based case-control study was designed to assess risk factors for CAP, including home exposure to passive smoking. All new cases of CAP in a well defined population were consecutively recruited during a 12 months period. The subgroup of never smokers was selected for the present analysis.

Results The study sample included 471 CAP patients and 532 controls who had never smoked. The annual incidence of CAP was estimated in 1.14 cases/10^3 inhabitants in passive smokers and 0.90 x10^{-3} in non-passive smokers (risk ratio [RR] 1.26; 95% confidence interval [CI]: 1.02-1.55) in the whole sample. In subjects ≥ 65 years old, this incidence was 2.50 x10^{-3} in passive smokers and 1.69 x10^{-3} in non-passive smokers (RR 1.48, 95% CI: 1.08-2.03). In this last age group, the percentage of passive smokers in cases and controls was 26.0% and 18.1%, respectively (P = 0.039), with a crude odds ratio (OR) of 1.59 (95% CI 1.02-2.38) and an adjusted (by age and sex) OR of 1.56 (95% CI 1.00-2.45).

Conclusions Passive smoking at home might be a risk factor for CAP in older adults (65 years or more).

Strengths and limitations of the study:

- The effect of passive smoking at home on CAP in adults is controversial
- The present study adds new evidence on this topic from a large population-based study.
- It shows a significant effect only in subjects 65 years old or over.
- Passive smoking was assessed by a self-reported questionnaire.

Introduction

Community-acquired pneumonia (CAP) is an important cause of morbidity and mortality in industrialized countries. In the general adult population, the annual incidence of CAP ranges between 1.6 and 13.4 cases per 1000 inhabitants, with a need for in-patient care between 22% and 51%, and a lethality of 3-24%, [1-3] which remain unchanged in recent years despite the use preventive measures.[4] There is strong evidence of an association between active tobacco smoking and the risk for CAP.[5-8] Tobacco not only has a direct and independent effect on the risk for CAP but also may act indirectly causing chronic bronchitis or chronic obstructive pulmonary disease (COPD), which in turn are well-recognized risk factors for CAP[8]. Therefore, one of the main action for preventing CAP is smoking cessation interventions.

There has been also an increasing interest to assess the effects of passive smoking. Although some studies suggested that passive smoking may be associated with a higher risk of respiratory infections in both children whose parents smoke [9-11] and adults,[12,13] the effect of exposure to passive smoking on CAP is still unclear. In most developed countries, exposure to tobacco smoke has been reduced in approximately 20-25% due to smoking bands, which prohibit tobacco smoking in workplaces and outdoor public areas.[13] However, tobacco laws prohibiting smoking in workplaces and leisure spaces do not have any influence on tobacco consumption at the home environment. This study was aimed to assess the influence of passive smoking exposure at home on the occurrence of CAP in adults.

Patients and methods

A population-based case-control study designed to identify risk factors for CAP (PACAP study) was conducted in an extensive rural and urban area on the eastern coast

of Spain, with predominantly Mediterranean climatic conditions. Details of the study have been previously published.[14] An initial prospective phase allowed to identify all new cases of CAP diagnosed during 1-year period and to estimate the incidence of CAP in the target population, which included 859,033 inhabitants older than 14 years assigned to any of the 64 participating primary care centers. Control subjects were frequency matched by age (± 5 years), sex, and primary health care area with cases. Controls were selected at random from the databases of the primary care centers. For the identification of cases, an active and exhaustive search of all cases of clinically suspected CAP presented over 1-year period was conducted. To this purpose, an active surveillance system was established to ensure the identification of all cases of CAP diagnosed in public and private health care facilities in the study area. Predefined criteria for case registration were based on acute lower respiratory tract infection, for which antibiotics had been prescribed, in association with the appearance of new or previously unknown focal signs on physical examination and radiography of the chest. All cases of CAP were periodically re-evaluated by chest radiography at monthly intervals until complete recovery. Patients with suspicion of CAP in which another noninfectious respiratory disease was later confirmed were excluded from the study, as were patients with active tuberculosis, aspiration pneumonia, and health care-associated pneumonia. Cases of CAP were followed during 4 weeks or until complete recovery. A questionnaire on CAP risk factors was administered to cases and controls at home. When the participant could not directly answer the questions (cognitive impairment, disease, or, for CAP cases, death), the questionnaire was administered to the closest family member or caregiver. The interviewers were physicians or nurses trained in interview techniques and in the administration of the study questionnaire. The instrument was structured into three sections related to the following aspects: a) health habits and lifestyle; b) chronic

respiratory diseases and other clinical conditions, and c) regular treatments during the last year. History of tobacco use, and passive smoking at work and at home were also recorded. Passive tobacco consumption was assessed by the question: ”Do you currently live with one or more smokers at home?” with two (yes/no) possible answers. All participants gave written informed consent. The study protocol was approved by the Ethics Committee of the *Consorci Sanitari del Maresme* (Barcelona, Spain).

Data analysis

For the purpose of this analysis, only cases and controls who never smoked were selected. Subjects were further classified into passive smokers at home and non-passive smokers at home. The effect of passive smoking exposure at home on CAP was assessed by two strategies as follows: a) estimation of the annual incidence of CAP in passive and non-passive smokers and calculation of the relative risk (RR) and its 95% confidence interval (CI) using data of the prospective phase of the study; and b) estimation of the odds ratio (OR) and its 95% CI by logistic regression analysis using data of the case-control study. To estimate the incidence of CAP in subjects exposed and non-exposed to passive smoking, it was assumed that the proportion of passive and non-passive smokers at home in each age and sex group of the study population was the same than that observed in the control group sample, considered highly representative of the study population because its random selection from primary care databases and with a 99.3% of population coverage.[15] In the control group (n=1326), overall prevalence of never smokers was 48.5% and the prevalence of passive smokers at home was 10.6% (or 26.3% of never smokers). These data were stratified by age and sex groups and applied to the general population distribution (Catalan Statistics Institute, www.idescat.cat) to determine the denominators (total population at risk) in the estimation of the CAP incidence. Moreover,

the attributable risk (AR; exposed risk - non-exposed risk) and the etiologic fraction in exposed population (EF%; [exposed risk - non-exposed risk]·100/exposed risk) were estimated as impact measures of passive smoking. Regarding the case-control study, OR was adjusted by age and sex since, in this analysis matching was broken when selecting only never smokers. Also, all analyses were made for the overall study population and stratifying by < 65 and ≥ 65 years of age. The Statistical Package for the Social Sciences (SPSS, version 15.0) was used for the analysis of data. Statistical significance was set at $P < 0.05$, or in the RR and OR estimations if the 95% CI did not include 1.0.

Results

A total of 1003 subjects who never smoked were selected from the PACAP database study, 283 (28.2%) of which reported to be in contact with tobacco smoke at home and were classified as passive smokers at home. Standardized prevalence of passive smoking at home in the study population was estimated at 28.4%. The comparison of the percentage of passive smokers between cases and controls did not show statistically significant differences either in the overall study sample (30.4% *vs* 26.3%, P=0.155) or in the subset of subjects younger than 65 years (46.1% *vs* 33.8%, P=0.931). However, in subjects aged 65 years or older, the percentage of passive smokers was significantly higher in cases with CAP than in controls (26.0% *vs* 18.1%, P=0.039). Table 1 shows the effect (OR) of passive smoking on CAP for the overall study sample and for the age subgroups, with a significant effect only in subjects aged 65 years or more, with an OR that remained almost invariable after adjusting by age and sex. In the study sample passive smoking exposure at home was not associated to other known risk factors for CAP, such as chronic bronchitis, COPD, upper respiratory tract infection in the previous month, hospital admission in the previous 5 years, history of any previously confirmed

pneumonia, sudden changes of temperature in the workplace in the previous 3 months, so that passive tobacco consumption was not adjusted by these variables.

The annual incidence of CAP in subjects exposed and non-exposed to passive smoking in home environment, Risk Ratio (RR), Attributable Risk (AR), and Etiologic Fraction (EF) for the overall study sample and for subgroups of age is summarized in Table 2. A statistically significant effect of passive tobacco exposure was observed in subjects aged 65 years or older; in which passive smoking carry a 48% increase in the risk for CAP.

Discussion

The results of the present analysis show that in adult general population passive exposure to tobacco smoke at home is not a risk factor for CAP, but in 65 year subjects or older passive smokers are at higher risk for CAP than non-exposed subjects, with an OR of 1.59. There is abundant scientific evidence on the effect of tobacco on CAP but evidence on the effect of passive smoking is scarcer. It is well known that smoking is one of the main independent risk factor for CAP and determines its severity. [7,16-18] This risk is directly associated with the number of cigarettes smoked and it is reduced after quitting.[8] Probably this may be explained by structural pulmonary lesions and alterations of the immune response, both innate and adaptative, as a result of smoking [19,20] which may favour the presence and propagation of microorganisms in the bronchial tree. Also, tobacco consumption increases tissue oxidative stress especially in the lung provoking lesions in the respiratory epithelium, connective tissue and vascular endothelium, which may increase their sensitivity to the inflammatory aggression of the infection,[19-21] even at low concentrations of smoke.[22] For these profuse

mechanisms, tobacco smoke may be an important risk factor for CAP also in passive smokers.[9,10]

The effect of passive smoking on the risk of CAP has been previously reported in patients older than 65 years requiring in-patient care for CAP [12] and in patients with pneumococcal bacteremia between 18 and 64 years of age.[11] However, the influence of passive smoking exposure on the appearance of CAP in adults of all ages on the basis of a population-based study was not well-known and uncertain. Nuorti JP et al.[11] showed that smoking was the main independent risk factor for invasive pneumococcal disease in immunocompetent adults aged between 18 and 64 years, with an OR of 4.1 in active smokers and 2.5 in passive smokers. In the present study, exposure to passive smoking at the home environment only showed an effect in subjects 65 years or over, in which a 59% risk excess was observed. Age seems to modify the effect of passive smoking on CAP. In older persons, the defense mechanisms may be more impaired and outweighed by this aggression. By contrast, in younger subjects, specific and nonspecific defense mechanisms may counterbalance the aggression of tobacco smoke provoked by other smokers.

The prevalence of passive smokers at home observed in the present study is very similar to those previously published regarding Spanish population in 2005 (29.5%), previously to entering into force the smoking ban,[23] which reinforce the reliability of the present data. This prevalence indicates the magnitude of the exposure to a factor which has a remarkable impact on the risk of CAP. Thus, approximately one third of pneumonic episodes in passive smokers >65 years of age are due to exposure to tobacco smoke from other persons at home and could be avoided if this factor was eliminated. The present findings, together with the evidence of the effectiveness of pneumococcal vaccine [24,25], in particular, the conjugate vaccine,[26] suggest that vaccination could

be administered not only to active smokers, but also to subjects older than 65 years of age exposed to passive smoking in the household environment.

In summary, the effect of passive smoking on CAP in adults is controversial. The present study adds new evidence on this topic from a population-based study and shows a significant effect only in subjects 65 years old or over, whose pulmonary defense mechanisms may be impaired or debilitated. These results must be taken into account when considering preventive measures for CAP in this specific age population, such as vaccination or changes in life style factors.

Support statement

Fondo de Investigaciones Sanitarias (FIS 99 / 0002-01) and CIBER de Respiratorio 06/06/0028 Madrid, Spain.

Conficts of interest statement

None to be declared

Authors' contributions to the study

JA, MSP, IB and AT have designed the study, contributed in the field work and write the manuscript

EP has performed the statistical analysis

JR, IH, EC, MA, PA and AE contributed in the field work

JA is the guarantor of the study.

Acknowledgements

The authors thank Marta Pulido, MD, for editing the manuscript and editorial assistance. The fees of medical editing were supported by Fundació Privada Salut del Consorci Sanitari del Maresme.

Data sharing statement

No additional data available.

Category: Original Research

other derivative work(s) based on the Contribution, iv) to exploit all subsidiary rights in the Contribution, v) the inclusion of electronic links from the Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above."

"All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: all authors had financial support from Fondo de Investigaciones Sanitarias (FIS 99/0002-01) and CIBER de Respiratorio 06/06/0028 for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work."

References

1. Woodhead MA, Macfarlane JT, McCracken JS, et al. Prospective study of the aetiology and outcome of pneumonia in the community. *Lancet* 1987;1:671-674.
2. Jokinen C, Heiskanen L, Juvonen H, et al. Incidence of community-acquired pneumonia in the population of four municipalities in eastern Finland. *Am J Epidemiol* 1993;137:977-988.
3. Oseasohn R, Skipper BE, Tempest B. Pneumonia in a Navajo community: a two-year experience. *Am Rev Respir Dis* 1978;117:1003-1009.
4. Gil-Prieto R, García-García L, Álvaro-Meca A, et al. The burden of hospitalisations for community-acquired pneumonia (CAP) and pneumococcal pneumonia in adults in Spain (2003–2007). *Vaccine* 2011;29:412-416.
5. Arcavi L, Benowitz NL. Cigarette smoking and infection. *Arch Intern Med* 2004; 164: 2206-2216.
6. Hoffman LH, Strutton DR, Stang PE, et al. Impact of smoking on respiratory illness-related outpatient visits among 50-to 75-year-old in the United States. *Clin Ther* 2002;24:317-324.
7. Almirall J, Bolíbar I, X. Balanzó X, et al. Risk factors for community-acquired pneumonia in adults: a population-based case control study. *Eur Respir J* 1999;13:349-355.
8. Almirall J, González CA, Balanzó X, et al. Proportion of community-acquired pneumonia cases attributable to tobacco smoking. *Chest* 1999;116:375-379.
9. Vinogradova Y, Hippisley-Cox J, Coupland C. Identification of new risk factors for pneumonia: population-based case-control study. *Br J Gen Pract* 2009;59:e882-e887.

10. Jones LL, Hashim A, McKeever T, et al. Parental and household smoking and the increased risk of bronchitis, bronchiolitis and other lower respiratory infections in infancy: systematic review and meta-analysis. *Respir Res* 2011;12:5, doi: 10.1186/1465-9921-12-5.
11. Nuorti JP, Butler JC, Farley MM, et al. Active bacterial core surveillance team. Cigarette smoking and invasive pneumococcal disease. *N Engl J Med* 2000;342:681-689.
12. Loeb M, Neupane B, Walter SD, et al. Environmental risk factors for community-acquired pneumonia hospitalization in older adults. *J Am Geriatr Soc* 2009;57:1036-1040.
13. Jiménez-Ruiz CA, Miranda JA, Hurt RD, et al. Study of the impact of laws regulating tobacco consumption on the prevalence of passive smoking in Spain. *Eur J Public Health* 2008;18:622-625.
14. Almirall J, Bolibar I, Serra-Prat M, et al. Community-Acquired Pneumonia in Catalan Countries (PACAP) Study Group. New evidence of risk factors for community-acquired pneumonia: a population-based study. *Eur Resp J* 2008;31:1274-1284.
15. http://www20.gencat.cat/docs/salut/Home/El%20Departament/Estadistiques%20sanitaries/Enquestes/02_enquesta_catalunya_continua/Documents/Arxius/informeesca2012.pdf
16. Pastor P, Medley F, Murphy TV. Invasive pneumococcal disease in Dallas County, Texas: results from population-based surveillance in 1995. *Clin Infect Dis* 1998;26:590-595.

17. Garcia-Vidal C, Ardanuy C, Tubau F, et al. Pneumococcal pneumonia presenting with septic shock: host- and pathogen-related factors and outcomes. *Thorax* 2010;65:77-81.

18. Marrie TJ, Shariatzadeh MR. Community-acquired pneumonia requiring admission to an intensive care unit: a descriptive study. *Medicine (Baltimore)* 2007;86:103-111.

19. Hodge S, Hodge GI, Ahern J, et al. Smoking alters alveolar macrophage recognition and phagocytic ability. *Am J Respir Cell Mol Biol* 2007;37:748-755.

20. Huttunen R, Heikkinen T, Syrjänen J. Smoking and the outcome of infection. *J Intern Med* 2011;269:258-269.

21. Arnson Y, Shoenfeld Y, Amital H. Effects of tobacco smoke on immunity, inflammation and autoimmunity. *J Autoimmun* 2010;34:J258-J265.

22. Strulovici-Barel Y, Omberg L, O'Mahony M, et al. Threshold of biologic responses of the small airway epithelium to low levels of tobacco smoke *Am J Respir Crit Care Med* 2010;182:1524-1532.

23. Jiménez-Ruiz CA, Miranda JAR, Hurt RD, et al. Study of the impact of laws regulating tobacco consumption on the prevalence of passive smoking in Spain. Eur J Public Health 2008;18:622-625.

24. Pearson WS, Dube SR, Ford ES, et al. Influenza and pneumococcal vaccination rates among smokers: data from the 2006. Behavioral Risk Factor Surveillance System. *Prev Med* 2009;48:180-183.

25. Centers for Disease Control and Prevention. Recommended adult immunization schedule. United States. 2011 Proposed Revisions. Advisory Committee on Immunization Practices. October 28, 2010

26. De Roux A, Schmöele-Thoma TR, Siber GR, et al. Comparison of pneumococcal conjugate polysaccharide and free polysaccharide vaccines in elderly adults :

conjugate vaccine elicits improved antibacterial immune responses and immunological memory. *Clin Infect Dis* 2008;46:1015-1023.

Table 1. Effect of passive tobacco consumption at home on the risk of CAP

Passive smoker	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)*
Overall study population	1.22 (0.93-1.61)	1.18 (0.90-1.57)
Subjects < 65 years	1.02 (0.71-1.46)	0.98 (0.68-1.41)
Subjects ≥ 65 years	1.59 (1.02-2.48)	1.56 (1.00-2.45)

*Effect adjusted by age and sex.

Table 2. Incidence of CAP and the impact of exposure to passive smoking at home

Never smokers	Annual incidence of CAP	Relative risk (95% CI)	Attributable risk (95% CI)	Etiologic fraction %
Overall study population				
Passive smokers	$1.14/10^3$ inhabitants	1.26 (1.02-1.55)	$0.235/10^3$ inhabitants (0.234-0.235)	20.6
Non-passive smokers	$0.90/10^3$ inhabitants			
Subjects aged < 65 years				
Passive smokers	$0.75/10^3$ inhabitants	1.14 (0.87-1.51)	$0.094/10^3$ inhabitants (0.094-0.095)	12.5
Non-passive smokers	$0.66/10^3$ inhabitants			
Subjects aged ≥ 65 years				
Passive smokers	$2.50/10^3$ inhabitants	1.48 (1.08-2.03)	$0.811/10^3$ inhabitants (0.810-0.812)	32.5
Non-passive smokers	$1.69/10^3$ inhabitants			

CAP: Community acquired pneumonia. CI: confidence interval.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract YES (see page 3: abstract)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found YES (see structured abstract in page 3)
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Yes (page 4)
Objectives	3	State specific objectives, including any prespecified hypotheses Yes (page 4)
Methods		
Study design	4	Present key elements of study design early in the paper: YES (page 4)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection: YES (page 5-6)
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up NO *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls: **YES** (page 5-6) *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants: No
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case: YES (page 5)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable: YES (page 5-6)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group: YES (page 5)
Bias	9	Describe any efforts to address potential sources of bias: YES (page 5)
Study size	10	Explain how the study size was arrived at: YES (page 5)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why: YES (page 6-7)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding: YES (page 6-7)
		(*b*) Describe any methods used to examine subgroups and interactions: YES (pages 6-7)
		(*c*) Explain how missing data were addressed: YES (pages 6-7)
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed: YES (page 5) *Cross-sectional study*—If applicable, describe analytical methods taking account of

	sampling strategy
	(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. YES (page 7)
		(b) Give reasons for non-participation at each stage YES (page 5)
		(c) Consider use of a flow diagram. NO
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. No (previously published)
		(b) Indicate number of participants with missing data for each variable of interest. YES (page 7)
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure YES (page 7-8, and tables 1 and 2)
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included. YES (page 7-8)
		(*b*) Report category boundaries when continuous variables were categorized. YES (see page 7-8)
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period. YES (see table 2)
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses. YES (page 7-8)
Discussion		
Key results	18	Summarise key results with reference to study objectives YES (page 8)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias. No
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. YES (page 8-10)
Generalisability	21	Discuss the generalisability (external validity) of the study results. YES (page 8-10)
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based. YES (page 11)

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Passive smoking at home is a risk factor for community-acquired pneumonia in older adults: a population-based case-control study

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-005133.R1
Article Type:	Research
Date Submitted by the Author:	15-May-2014
Complete List of Authors:	Almirall, Jordi; Hospital de Mataro, Intensive Care Unit Serra-Prat, Mateu; Hospital de Mataró, Research Unit Bolibar, Ignasi; IIB Sant Pau, Clinical Epidemiology and Public Health, Institut de Recerca Biomedica Palomera, Elisabet; Consorci Sanitari del Maresme, Unitat de Recerca Roig, Jordi; Hospital Nostra Senyora de Meritxell, Pneumologia Hospital, Imma; 5Institut Català de la Salut (ICS),, ABS Valls Carandell, Eugenia; IB-SALUT Balears, Agustí, Mercè; Institut Català de la Salut (ICS), ABS Targue Ayuso, Pilar; INSALUD, Valencia, Estela, Andreu; IB-SALUT Balears, Torres, Antoni; Hospital Clinic i Provincial, Pneumology
Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Epidemiology, Public health
Keywords:	EPIDEMIOLOGY, Public health < INFECTIOUS DISEASES, Infection control < INFECTIOUS DISEASES, Thoracic medicine < INTERNAL MEDICINE

Category: Original Research

"All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: all authors had financial support from Fondo de Investigaciones Sanitarias (FIS 99/0002-01) and CIBER de Respiratorio 06/06/0028 for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work."

Passive smoking at home is a risk factor for community-acquired pneumonia in older adults: a population-based case-control study.

Jordi Almirall[1], Mateu Serra-Prat[2], Ignasi Bolíbar[3], Elisabet Palomera[2], Jordi Roig[4], Imma Hospital[5], Eugenia Carandell[6], Mercè Agustí[5], Pilar Ayuso[7], Andreu Estela[6], Antoni Torres[8] and the Study Group of Community-Acquired Pneumonia in Catalan Countries (PACAP)

[1]Critical Care Unit, Hospital de Mataró, Universitat Autònoma de Barcelona, Ciber Enfermedades Respiratorias, CIBERES, Barcelona, Spain.

[2]Research Unit, Hospital de Mataró. CIBEREHD, Barcelona, Spain.

[3]Department of Clinical Epidemiology and Public Health, Institut de Recerca Biomedica (IIB Sant Pau) Barcelona, Universitat Autònoma de Barcelona, CIBERESP, Barcelona, Spain.

[4]Hospital Nostra Senyora de Meritxell, Principat d'Andorra.

[5]Institut Català de la Salut (ICS), Barcelona, Spain.

[6]IB-SALUT Balears, Palma de Mallorca, Spain.

[7]INSALUD, Valencia, Spain.

[8]Service of Pneumology, Institut Clínic del Torax, IDIBAPS, Hospital Clínic de Barcelona. Universitat de Barcelona, CIBERES, Barcelona, Spain.

J. Almirall, e-mail: jalmirall@csdm.cat
M. Serra-Prat, e-mail: mserra@csdm.cat
I. Bolíbar, e-mail: ibolibar@santpau.es
E. Palomera, e-mail: epalomera@csdm.cat
J. Roig, e-mail: averoig@mypic.ad
I. Hospital, e-mail: ihospitalg.tarte.ics@gencat.cat
E. Carandell, e-mail: ecarandell@ibsalut.caib.es
M. Agustí, e-mail: magustip@telefonica.net
P. Ayuso, e-mail: payuso77@hotmail.com
A. Estela, e-mail: andreu.estela@ssib.es
A. Torres, e-mail: atorres@clinic.ub.es

Correspondence to: Dr. Jordi Almirall, Intensive Care Unit, Hospital de Mataró, Carretera de Cirera s/n, E-08304 Mataró, Barcelona, Spain. Telephone number +34 93 7417700, fax +34 93 7417770, e-mail: jalmirall@csdm.cat

Keywords: Community-acquired pneumonia, passive smoking, older adults.

Word count: 1963.

Abstract

Objective: To assess whether passive smoking exposure at home is a risk factor for community-acquired pneumonia (CAP) in adults.

Setting: A population-based case-control study was designed in a Mediterranean area with 860.000 inhabitants >14 years.

Participants: 1003 subjects who never smoked were recruited.

Primary and secondary outcome measures: risk factors for CAP, including home exposure to passive smoking were registered. All new cases of CAP in a well defined population were consecutively recruited during a 12 months period.

Methods A population-based case-control study was designed to assess risk factors for CAP, including home exposure to passive smoking. All new cases of CAP in a well defined population were consecutively recruited during a 12 months period. The subgroup of never smokers was selected for the present analysis.

Results The study sample included 471 CAP patients and 532 controls who had never smoked. The annual incidence of CAP was estimated in 1.14 cases $x10^{-3}$ inhabitants in passive smokers and 0.90 $x10^{-3}$ in non-passive smokers (risk ratio [RR] 1.26; 95% confidence interval [CI]: 1.02-1.55) in the whole sample. In subjects ≥ 65 years old, this incidence was 2.50 $x10^{-3}$ in passive smokers and 1.69 $x10^{-3}$ in non-passive smokers (RR 1.48, 95% CI: 1.08-2.03). In this last age group, the percentage of passive smokers in cases and controls was 26.0% and 18.1%, respectively (P = 0.039), with a crude odds ratio (OR) of 1.59 (95% CI 1.02-2.38) and an adjusted (by age and sex) OR of 1.56 (95% CI 1.00-2.45).

Conclusions Passive smoking at home is a risk factor for CAP in older adults (65 years or more).

Strengths and limitations of the study:

- **The effect of passive smoking at home on CAP in adults is controversial**
- **The present findings adds new evidence of the unfavourable effect of exposure to passive smoking at home based on data from a large population-based study**
- **It shows a significant effect only in subjects aged 65 years or older**
- **Passive smoking was assessed by a self-reported questionnaire which could lead to an imprecise exposure quantitative measure.**
- **Key messages**
- - What is the key question?
- Is passive smoking exposure at home a risk factor for community-acquired pneumonia in adults?
- - What is the bottom line?
- Passive smoking at home is a risk factor for CAP in older adults (65 years or more).
- - Why read on?
- The effect of passive smoking on CAP in adults is controversial, and the present population-based study adds new evidence on this topic.

Introduction

Community-acquired pneumonia (CAP) is an important cause of morbidity and mortality in industrialized countries. In the general adult population, the annual incidence of CAP ranges between 1.6 and 13.4 cases per 1000 inhabitants, with a need for in-patient care between 22% and 51%, and a lethality of 3-24%, [1-3] which remain unchanged in recent years despite the use preventive measures.[4] There is strong evidence of an association between active tobacco smoking and the risk for CAP.[5-8] Tobacco not only has a direct and independent effect on the risk for CAP but also may act indirectly causing chronic bronchitis or chronic obstructive pulmonary disease (COPD), which in turn are well-recognized risk factors for CAP[8]. Therefore, one of the main action for preventing CAP is smoking cessation interventions.

There has been also an increasing interest to assess the effects of passive smoking. Although some studies suggested that passive smoking may be associated with a higher risk of respiratory infections in both children whose parents smoke [9-11] and adults,[12,13] the effect of exposure to passive smoking on CAP is still unclear. In most developed countries, exposure to tobacco smoke has been reduced in approximately 20-25% due to smoking bands, which prohibit tobacco smoking in workplaces and outdoor public areas.[13] However, tobacco laws prohibiting smoking in workplaces and leisure spaces do not have any influence on tobacco consumption at the home environment. This study was aimed to assess the influence of passive smoking exposure at home on the occurrence of CAP in adults.

Patients and methods

A population-based case-control study designed to identify risk factors for CAP (PACAP study) was conducted in an extensive rural and urban area on the eastern coast

of Spain, with predominantly Mediterranean climatic conditions. Details of the study have been previously published.[14] An initial prospective phase allowed to identify all new cases of CAP diagnosed during 1-year period and to estimate the incidence of CAP in the target population, which included 859,033 inhabitants older than 14 years assigned to any of the 64 participating primary care centers. Control subjects were frequency matched by age (± 5 years), sex, and primary health care area with cases. Controls were selected at random from the databases of the primary care centers. For the identification of cases, an active and exhaustive search of all cases of clinically suspected CAP presented over 1-year period was conducted. To this purpose, an active surveillance system was established to ensure the identification of all cases of CAP diagnosed in public and private health care facilities in the study area. Predefined criteria for case registration were based on acute lower respiratory tract infection, for which antibiotics had been prescribed, in association with the appearance of new or previously unknown focal signs on physical examination and radiography of the chest. All cases of CAP were periodically re-evaluated by chest radiography at monthly intervals until complete recovery. Patients with suspicion of CAP in which another noninfectious respiratory disease was later confirmed were excluded from the study, as were patients with active tuberculosis, aspiration pneumonia, and health care-associated pneumonia. Cases of CAP were followed during 4 weeks or until complete recovery. A questionnaire on CAP risk factors was administered to cases and controls at home. When the participant could not directly answer the questions (cognitive impairment, disease, or, for CAP cases, death), the questionnaire was administered to the closest family member or caregiver. The interviewers were physicians or nurses trained in interview techniques and in the administration of the study questionnaire. The instrument was structured into three sections related to the following aspects: a) health habits and lifestyle; b) chronic

respiratory diseases and other clinical conditions, and c) regular treatments during the last year. History of tobacco use, and passive smoking at work and at home were also recorded. Passive tobacco consumption was assessed by the question: "Do you currently live with one or more smokers at home?" with two (yes/no) possible answers. All participants gave written informed consent. The study protocol was approved by the Ethics Committee of the *Consorci Sanitari del Maresme* (Barcelona, Spain).

Data analysis

For the purpose of this analysis, only cases and controls who never smoked were selected. Subjects were further classified into passive smokers at home and non-passive smokers at home. The effect of passive smoking exposure at home on CAP was assessed by two strategies as follows: a) estimation of the annual incidence of CAP in passive and non-passive smokers and calculation of the relative risk (RR) and its 95% confidence interval (CI) using data of the prospective phase of the study; and b) estimation of the odds ratio (OR) and its 95% CI by logistic regression analysis using data of the case-control study. To estimate the incidence of CAP in subjects exposed and non-exposed to passive smoking, it was assumed that the proportion of passive and non-passive smokers at home in each age and sex group of the study population was the same than that observed in the control group sample, considered highly representative of the study population because its random selection from primary care databases and with a 99.3% of population coverage.[15] In the control group (n=1326), overall prevalence of never smokers was 48.5% and the prevalence of passive smokers at home was 10.6% (or 26.3% of never smokers). These data were stratified by age and sex groups and applied to the general population distribution (Catalan Statistics Institute, www.idescat.cat) to determine the denominators (total population at risk) in the estimation of the CAP incidence. Moreover,

the attributable risk (AR; exposed risk - non-exposed risk) and the etiologic fraction in exposed population (EF%; [exposed risk - non-exposed risk]·100/exposed risk) were estimated as impact measures of passive smoking. Regarding the case-control study, OR was adjusted by age and sex since, in this analysis matching was broken when selecting only never smokers. Also, all analyses were made for the overall study population and stratifying by < 65 and ≥ 65 years of age. The Statistical Package for the Social Sciences (SPSS, version 15.0) was used for the analysis of data. Statistical significance was set at $P < 0.05$, or in the RR and OR estimations if the 95% CI did not include 1.0.

Results

A total of 1003 subjects who never smoked were selected from the PACAP database study, 283 (28.2%) of which reported to be in contact with tobacco smoke at home and were classified as passive smokers at home. Among cases, 75% were females (median age: 65 years, range 14-96), while 71% of controls were females (median age: 63 years, range 15-100). Standardized prevalence of passive smoking at home in the study population was estimated at 28.4%. The comparison of the percentage of passive smokers between cases and controls did not show statistically significant differences either in the overall study sample (30.4% *vs* 26.3%, P=0.155) or in the subset of subjects younger than 65 years (46.1% *vs* 33.8%, P=0.931). However, in subjects aged 65 years or older, the percentage of passive smokers was significantly higher in cases with CAP than in controls (26.0% *vs* 18.1%, P=0.039). Table 1 shows the effect (OR) of passive smoking on CAP for the overall study sample and for the age subgroups, with a significant effect only in subjects aged 65 years or more, with an OR that remained almost invariable after adjusting by age and sex. In the study sample passive smoking exposure at home was not associated with other known risk factors for CAP,

such as chronic bronchitis, COPD, upper respiratory tract infection in the previous month, hospital admission in the previous 5 years, history of any previously confirmed pneumonia, sudden changes of temperature in the workplace in the previous 3 months, so that passive tobacco consumption was not adjusted by these variables.

The annual incidence of CAP in subjects exposed and non-exposed to passive smoking in home environment, Risk Ratio (RR), Attributable Risk (AR), and Etiologic Fraction (EF) for the overall study sample and for subgroups of age is summarized in Table 2. A statistically significant effect of passive tobacco exposure was observed in subjects aged 65 years or older; in which passive smoking carry a 48% increase in the risk for CAP.

Discussion

The results of the present analysis show that age modify the effect of passive smoking on CAP. In 65 year subjects or older passive smokers are at higher risk for CAP than non-exposed subjects, with an OR of 1.59, while this effect disappeared in subjects under 65 years of age. There is abundant scientific evidence on the effect of tobacco on CAP but evidence on the effect of passive smoking is scarcer. It is well known that smoking is one of the main independent risk factor for CAP and determines its severity. [7,16-18] This risk is directly associated with the number of cigarettes smoked and it is reduced after quitting.[8] Probably this may be explained by structural pulmonary lesions and alterations of the immune response, both innate and adaptative, as a result of smoking [19,20] which may favour the presence and propagation of microorganisms in the bronchial tree. Also, tobacco consumption increases tissue oxidative stress especially in the lung provoking lesions in the respiratory epithelium, connective tissue and vascular endothelium, which may increase their sensitivity to the inflammatory

aggression of the infection,[19-21] even at low concentrations of smoke.[22] For these profuse mechanisms, tobacco smoke may be an important risk factor for CAP also in passive smokers.[9,10]

The effect of passive smoking on the risk of CAP has been previously reported in patients older than 65 years requiring in-patient care for CAP [12] and in patients with pneumococcal bacteremia between 18 and 64 years of age.[11] However, the influence of passive smoking exposure on the appearance of CAP in adults of all ages on the basis of a population-based study was not well-known and uncertain. Nuorti JP et al.[11] showed that smoking was the main independent risk factor for invasive pneumococcal disease in immunocompetent adults aged between 18 and 64 years, with an OR of 4.1 in active smokers and 2.5 in passive smokers. In the present study, exposure to passive smoking at the home environment only showed an effect in subjects 65 years or over, in which a 59% risk excess was observed. Age seems to modify the effect of passive smoking on CAP but it is not clear if this interaction is due to age "per se" or if it is due to a more prolonged exposure or a different exposure pattern or intensity to passive tobacco smoke at home in elderly subjects. Moreover, in older persons the defense mechanisms may be more impaired and outweighed by this aggression. By contrast, in younger subjects, specific and nonspecific defense mechanisms may counterbalance the aggression of tobacco smoke provoked by other smokers.

The prevalence of passive smokers at home observed in the present study is very similar to those previously published regarding Spanish population in 2005 (29.5%), previously to entering into force the smoking ban,[23] which reinforce the reliability of the present data. This prevalence indicates the magnitude of the exposure to a factor which has a remarkable impact on the risk of CAP. Thus, approximately one third of

pneumonic episodes in passive smokers >65 years of age are due to exposure to tobacco smoke from other persons at home and could be avoided if this factor was eliminated. The present findings, together with the evidence of the effectiveness of pneumococcal vaccine [24,25], in particular, the conjugate vaccine,[26] suggest that vaccination could be administered not only to active smokers, but also to subjects older than 65 years of age who cannot quit to be exposed to passive smoking in the household environment. The main study limitation include the inaccuracy for quantitative measuring passive tobacco smoke exposure since, for example, exposure intensity was not considered and co-inhabitats who smoke at home may go to smoke outside. However, this circumstance was the same for cases and controls and, although it may have diluted the expected effect, a bias was not introduced. We have not taken into account passive exposure at work or in public places, which are now forbidden but were allowed when the study was conducted, because our aim was focused on the effect of passive smoking at home.

In summary, the present study adds new evidence on the effect of passive smoking on CAP in adults from a population-based study. It shows a significant effect only in subjects 65 years old or over, who may be exposed for a more prolonged period of time, with a more intensive pattern of exposure and whose pulmonary defense mechanisms may be impaired or debilitated. These results must be taken into account when considering preventive measures for CAP in this specific age population, such as changes in life style factors or vaccination.

Acknowledgements

The authors thank Marta Pulido, MD, for editing the manuscript and editorial assistance. The fees of medical editing were supported by Fundació Privada Salut del Consorci Sanitari del Maresme.

Support statement

Fondo de Investigaciones Sanitarias (FIS 99 / 0002-01) and CIBER de Respiratorio 06/06/0028 Madrid, Spain.

Authors' contributions to the study

JA, MSP, IB and AT have designed the study, contributed in the field work and write the manuscript

EP has performed the statistical analysis

JR, IH, EC, MA, PA and AE contributed in the field work

JA is the guarantor of the study.

Conficts of interest statement

None to be declared

Data Sharing Statement

No additional data available.

References

1. Torres A, Blasi F, Peetermans WE et al. The aetiology and antibiotic management of community-acquired pneumonia in adults in Europe: a literature review. *Eur J Clin Microbiol Infect Dis* 2014; DOI 10.1007/s10096-014-2067-1

2. Torres A, Peetermans WE, Viegi G, et al. Risk factors for community-acquired pneumonia in adults in Europe: a literature review. *Thorax* 2013; 68: 1057-1065

3. Oseasohn R, Skipper BE, Tempest B. Pneumonia in a Navajo community: a two-year experience. *Am Rev Respir Dis* 1978; 117: 1003-1009

4.Gil-Prieto R, García-García L, Álvaro-Meca A, et al. The burden of hospitalisations for community-acquired pneumonia (CAP) and pneumococcal pneumonia in adults in Spain (2003–2007). *Vaccine* 2011;29:412-416.

5.Arcavi L, Benowitz NL. Cigarette smoking and infection. *Arch Intern Med* 2004; 164: 2206-2216.

6. Hoffman LH, Strutton DR, Stang PE, et al. Impact of smoking on respiratory illness-related outpatient visits among 50-to 75-year-old in the United States. *Clin Ther* 2002;24:317-324.

7. Almirall J, Bolíbar I, X. Balanzó X, et al. Risk factors for community-acquired pneumonia in adults: a population-based case control study. *Eur Respir J* 1999;13:349-355.

8. Almirall J, González CA, Balanzó X, et al. Proportion of community-acquired pneumonia cases attributable to tobacco smoking. *Chest* 1999;116:375-379.

9. Vinogradova Y, Hippisley-Cox J, Coupland C. Identification of new risk factors for pneumonia: population-based case-control study. *Br J Gen Pract* 2009;59:e882-e887.

10. Jones LL, Hashim A, McKeever T, et al. Parental and household smoking and the increased risk of bronchitis, bronchiolitis and other lower respiratory infections in

infancy: systematic review and meta-analysis. *Respir Res* 2011;12:5, doi: 10.1186/1465-9921-12-5.

11. Nuorti JP, Butler JC, Farley MM, et al. Active bacterial core surveillance team. Cigarette smoking and invasive pneumococcal disease. *N Engl J Med* 2000;342:681-689.

12. Loeb M, Neupane B, Walter SD, et al. Environmental risk factors for community-acquired pneumonia hospitalization in older adults. *J Am Geriatr Soc* 2009;57:1036-1040.

13.Jiménez-Ruiz CA, Miranda JA, Hurt RD, et al. Study of the impact of laws regulating tobacco consumption on the prevalence of passive smoking in Spain. *Eur J Public Health* 2008;18:622-625.

14. Almirall J, Bolibar I, Serra-Prat M, et al. Community-Acquired Pneumonia in Catalan Countries (PACAP) Study Group. New evidence of risk factors for community-acquired pneumonia: a population-based study. *Eur Resp J* 2008;31:1274-1284.

15.http://www20.gencat.cat/docs/salut/Home/El%20Departament/Estadistiques%20sanitaries/Enquestes/02_enquesta_catalunya_continua/Documents/Arxius/informeesca2012.pdf

16. Pastor P, Medley F, Murphy TV. Invasive pneumococcal disease in Dallas County, Texas: results from population-based surveillance in 1995. *Clin Infect Dis* 1998;26:590-595.

17. Garcia-Vidal C, Ardanuy C, Tubau F, et al. Pneumococcal pneumonia presenting with septic shock: host- and pathogen-related factors and outcomes. *Thorax* 2010;65:77-81.

18. Marrie TJ, Shariatzadeh MR. Community-acquired pneumonia requiring admission to an intensive care unit: a descriptive study. *Medicine (Baltimore)* 2007;86:103-111.

19. Hodge S, Hodge GI, Ahern J, et al. Smoking alters alveolar macrophage recognition and phagocytic ability. *Am J Respir Cell Mol Biol* 2007;37:748-755.

20. Huttunen R, Heikkinen T, Syrjänen J. Smoking and the outcome of infection. *J Intern Med* 2011;269:258-269.

21. Arnson Y, Shoenfeld Y, Amital H. Effects of tobacco smoke on immunity, inflammation and autoimmunity. *J Autoimmun* 2010;34:J258-J265.

22. Strulovici-Barel Y, Omberg L, O'Mahony M, et al. Threshold of biologic responses of the small airway epithelium to low levels of tobacco smoke *Am J Respir Crit Care Med* 2010;182:1524-1532.

23. Jiménez-Ruiz CA, Miranda JAR, Hurt RD, et al. Study of the impact of laws regulating tobacco consumption on the prevalence of passive smoking in Spain. Eur J Public Health 2008;18:622-625.

24. Pearson WS, Dube SR, Ford ES, et al. Influenza and pneumococcal vaccination rates among smokers: data from the 2006. Behavioral Risk Factor Surveillance System. *Prev Med* 2009;48:180-183.

25. Centers for Disease Control and Prevention. Recommended adult immunization schedule. United States. 2011 Proposed Revisions. Advisory Committee on Immunization Practices. October 28, 2010

26. De Roux A, Schmöele-Thoma TR, Siber GR, et al. Comparison of pneumococcal conjugate polysaccharide and free polysaccharide vaccines in elderly adults : conjugate vaccine elicits improved antibacterial immune responses and immunological memory. *Clin Infect Dis* 2008;46:1015-1023.

Table 1. Effect of passive tobacco consumption at home on the risk of CAP

Passive smoker	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)*
Overall study population	1.22 (0.93-1.61)	1.18 (0.90-1.57)
Subjects < 65 years	1.02 (0.71-1.46)	0.98 (0.68-1.41)
Subjects ≥ 65 years	1.59 (1.02-2.48)	1.56 (1.00-2.45)

*Effect adjusted by age and sex.

Table 2. Incidence of CAP and the impact of exposure to passive smoking at home

Never smokers	Annual incidence of CAP	Relative risk (95% CI)	Attributable risk (95% CI)	Etiologic fraction %
Overall study population				
Passive smokers	1.14/10^3 inhabitants	1.26 (1.02-1.55)	0.235/10^3 inhabitants (0.234-0.235)	20.6
Non-passive smokers	0.90/10^3 inhabitants			
Subjects aged < 65 years				
Passive smokers	0.75/10^3 inhabitants	1.14 (0.87-1.51)	0.094/10^3 inhabitants (0.094-0.095)	12.5
Non-passive smokers	0.66/10^3 inhabitants			
Subjects aged ≥ 65 years				
Passive smokers	2.50/10^3 inhabitants	1.48 (1.08-2.03)	0.811/10^3 inhabitants (0.810-0.812)	32.5
Non-passive smokers	1.69/10^3 inhabitants			

CAP: Community acquired pneumonia. CI: confidence interval.

Category: Original Research

"All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: all authors had financial support from Fondo de Investigaciones Sanitarias (FIS 99/0002-01) and CIBER de Respiratorio 06/06/0028 for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work."

Passive smoking at home is a risk factor for community-acquired pneumonia in older adults: a population-based case-control study.

Jordi Almirall[1], Mateu Serra-Prat[2], Ignasi Bolíbar[3], Elisabet Palomera[2], Jordi Roig[4], Imma Hospital[5], Eugenia Carandell[6], Mercè Agustí[5], Pilar Ayuso[7], Andreu Estela[6], Antoni Torres[8] and the Study Group of Community-Acquired Pneumonia in Catalan Countries (PACAP)

[1]Critical Care Unit, Hospital de Mataró, Universitat Autònoma de Barcelona, Ciber Enfermedades Respiratorias, CIBERES, Barcelona, Spain.

[2]Research Unit, Hospital de Mataró. CIBEREHD, Barcelona, Spain.

[3]Department of Clinical Epidemiology and Public Health, Institut de Recerca Biomedica (IIB Sant Pau) Barcelona, Universitat Autònoma de Barcelona, CIBERESP, Barcelona, Spain.

[4]Hospital Nostra Senyora de Meritxell, Principat d'Andorra.

[5]Institut Català de la Salut (ICS), Barcelona, Spain.

[6]IB-SALUT Balears, Palma de Mallorca, Spain.

[7]INSALUD, Valencia, Spain.

[8]Service of Pneumology, Institut Clínic del Torax, IDIBAPS, Hospital Clínic de Barcelona. Universitat de Barcelona, CIBERES, Barcelona, Spain.

J. Almirall, e-mail: jalmirall@csdm.cat
M. Serra-Prat, e-mail: mserra@csdm.cat
I. Bolíbar, e-mail: ibolibar@santpau.es
E. Palomera, e-mail: epalomera@csdm.cat
J. Roig, e-mail: averoig@mypic.ad
I. Hospital, e-mail: ihospitalg.tarte.ics@gencat.cat
E. Carandell, e-mail: ecarandell@ibsalut.caib.es
M. Agustí, e-mail: magustip@telefonica.net
P. Ayuso, e-mail: payuso77@hotmail.com
A. Estela, e-mail: andreu.estela@ssib.es
A. Torres, e-mail: atorres@clinic.ub.es

Correspondence to: Dr. Jordi Almirall, Intensive Care Unit, Hospital de Mataró, Carretera de Cirera s/n, E-08304 Mataró, Barcelona, Spain. Telephone number +34 93 7417700, fax +34 93 7417770, e-mail: jalmirall@csdm.cat

Keywords: Community-acquired pneumonia, passive smoking, older adults.

Word count: 1963.

Key messages

- What is the key question?
Is passive smoking exposure at home a risk factor for community-acquired pneumonia in adults?
- What is the bottom line?
Passive smoking at home is a risk factor for CAP in older adults (65 years or more).
- Why read on?
The effect of passive smoking on CAP in adults is controversial, and the present population-based study adds new evidence on this topic.

Abstract

Background To assess whether passive smoking exposure at home is a risk factor for community-acquired pneumonia (CAP) in adults.

Setting: A population-based case-control study was designed in a Mediterranean area with 860.000 inhabitants >14 years.

Participants: 1003 subjects who never smoked were recruited.

Primary and secondary outcome measures: risk factors for CAP, including home exposure to passive smoking were registered. All new cases of CAP in a well defined population were consecutively recruited during a 12 months period.

~~**Methods** A population based case control study was designed to assess risk factors for CAP, including home exposure to passive smoking. All new cases of CAP in a well defined population were consecutively recruited during a 12 months period. The subgroup of never smokers was selected for the present analysis.~~

Results The study sample included 471 CAP patients and 532 controls who had never smoked. The annual incidence of CAP was estimated in 1.14 cases $x10^{-3}$ inhabitants in passive smokers and 0.90 $x10^{-3}$ in non-passive smokers (risk ratio [RR] 1.26; 95% confidence interval [CI]: 1.02-1.55) in the whole sample. In subjects ≥ 65 years old, this incidence was 2.50 $x10^{-3}$ in passive smokers and 1.69 $x10^{-3}$ in non-passive smokers (RR 1.48, 95% CI: 1.08-2.03). In this last age group, the percentage of passive smokers in cases and controls was 26.0% and 18.1%, respectively (P = 0.039), with a crude odds ratio (OR) of 1.59 (95% CI 1.02-2.38) and an adjusted (by age and sex) OR of 1.56 (95% CI 1.00-2.45).

Conclusions Passive smoking at home is a risk factor for CAP in older adults (65 years or more).

Formatted: Font: Not Bold, Not Italic, (Asian) Japanese

Formatted: Strikethrough

Strengths and limitations of the study:

- **The effect of passive smoking at home on CAP in adults is controversial**
- **The present findings adds new evidence of the unfavourable effect of exposure to passive smoking at home based on data from a large population-based study**
- **It shows a significant effect only in subjects aged 65 years or older**
- **Passive smoking was assessed by a self-reported questionnaire which could lead to an imprecise exposure quantitative measure.**

Introduction

Community-acquired pneumonia (CAP) is an important cause of morbidity and mortality in industrialized countries. In the general adult population, the annual incidence of CAP ranges between 1.6 and 13.4 cases per 1000 inhabitants, with a need for in-patient care between 22% and 51%, and a lethality of 3-24%, [1-3] which remain unchanged in recent years despite the use preventive measures.[4] There is strong evidence of an association between active tobacco smoking and the risk for CAP.[5-8] Tobacco not only has a direct and independent effect on the risk for CAP but also may act indirectly causing chronic bronchitis or chronic obstructive pulmonary disease (COPD), which in turn are well-recognized risk factors for CAP[8]. Therefore, one of the main action for preventing CAP is smoking cessation interventions.

There has been also an increasing interest to assess the effects of passive smoking. Although some studies suggested that passive smoking may be associated with a higher risk of respiratory infections in both children whose parents smoke [9-11] and adults,[12,13] the effect of exposure to passive smoking on CAP is still unclear. In most developed countries, exposure to tobacco smoke has been reduced in approximately 20-25% due to smoking bands, which prohibit tobacco smoking in workplaces and outdoor public areas.[13] However, tobacco laws prohibiting smoking in workplaces and leisure spaces do not have any influence on tobacco consumption at the home environment. This study was aimed to assess the influence of passive smoking exposure at home on the occurrence of CAP in adults.

Patients and methods

A population-based case-control study designed to identify risk factors for CAP (PACAP study) was conducted in an extensive rural and urban area on the eastern coast

of Spain, with predominantly Mediterranean climatic conditions. Details of the study have been previously published.[14] An initial prospective phase allowed to identify all new cases of CAP diagnosed during 1-year period and to estimate the incidence of CAP in the target population, which included 859,033 inhabitants older than 14 years assigned to any of the 64 participating primary care centers. Control subjects were frequency matched by age (± 5 years), sex, and primary health care area with cases. Controls were selected at random from the databases of the primary care centers. For the identification of cases, an active and exhaustive search of all cases of clinically suspected CAP presented over 1-year period was conducted. To this purpose, an active surveillance system was established to ensure the identification of all cases of CAP diagnosed in public and private health care facilities in the study area. Predefined criteria for case registration were based on acute lower respiratory tract infection, for which antibiotics had been prescribed, in association with the appearance of new or previously unknown focal signs on physical examination and radiography of the chest. All cases of CAP were periodically re-evaluated by chest radiography at monthly intervals until complete recovery. Patients with suspicion of CAP in which another noninfectious respiratory disease was later confirmed were excluded from the study, as were patients with active tuberculosis, aspiration pneumonia, and health care-associated pneumonia. Cases of CAP were followed during 4 weeks or until complete recovery. A questionnaire on CAP risk factors was administered to cases and controls at home. When the participant could not directly answer the questions (cognitive impairment, disease, or, for CAP cases, death), the questionnaire was administered to the closest family member or caregiver. The interviewers were physicians or nurses trained in interview techniques and in the administration of the study questionnaire. The instrument was structured into three sections related to the following aspects: a) health habits and lifestyle; b) chronic

respiratory diseases and other clinical conditions, and c) regular treatments during the last year. History of tobacco use, and passive smoking at work and at home were also recorded. Passive tobacco consumption was assessed by the question: "Do you currently live with one or more smokers at home?" with two (yes/no) possible answers. All participants gave written informed consent. The study protocol was approved by the Ethics Committee of the *Consorci Sanitari del Maresme* (Barcelona, Spain).

Data analysis

For the purpose of this analysis, only cases and controls who never smoked were selected. Subjects were further classified into passive smokers at home and non-passive smokers at home. The effect of passive smoking exposure at home on CAP was assessed by two strategies as follows: a) estimation of the annual incidence of CAP in passive and non-passive smokers and calculation of the relative risk (RR) and its 95% confidence interval (CI) using data of the prospective phase of the study; and b) estimation of the odds ratio (OR) and its 95% CI by logistic regression analysis using data of the case-control study. To estimate the incidence of CAP in subjects exposed and non-exposed to passive smoking, it was assumed that the proportion of passive and non-passive smokers at home in each age and sex group of the study population was the same than that observed in the control group sample, considered highly representative of the study population because its random selection from primary care databases and with a 99.3% of population coverage.[15] In the control group (n=1326), overall prevalence of never smokers was 48.5% and the prevalence of passive smokers at home was 10.6% (or 26.3% of never smokers). These data were stratified by age and sex groups and applied to the general population distribution (Catalan Statistics Institute, www.idescat.cat) to determine the denominators (total population at risk) in the estimation of the CAP incidence. Moreover,

the attributable risk (AR; exposed risk - non-exposed risk) and the etiologic fraction in exposed population (EF%; [exposed risk - non-exposed risk]·100/exposed risk) were estimated as impact measures of passive smoking. Regarding the case-control study, OR was adjusted by age and sex since, in this analysis matching was broken when selecting only never smokers. Also, all analyses were made for the overall study population and stratifying by < 65 and ≥ 65 years of age. The Statistical Package for the Social Sciences (SPSS, version 15.0) was used for the analysis of data. Statistical significance was set at $P < 0.05$, or in the RR and OR estimations if the 95% CI did not include 1.0.

Results

A total of 1003 subjects who never smoked were selected from the PACAP database study, 283 (28.2%) of which reported to be in contact with tobacco smoke at home and were classified as passive smokers at home. Among cases, 75% were females (median age: 65 years, range 14-96), while 71% of controls were females (median age: 63 years, range 15-100). Standardized prevalence of passive smoking at home in the study population was estimated at 28.4%. The comparison of the percentage of passive smokers between cases and controls did not show statistically significant differences either in the overall study sample (30.4% *vs* 26.3%, P=0.155) or in the subset of subjects younger than 65 years (46.1% *vs* 33.8%, P=0.931). However, in subjects aged 65 years or older, the percentage of passive smokers was significantly higher in cases with CAP than in controls (26.0% *vs* 18.1%, P=0.039). Table 1 shows the effect (OR) of passive smoking on CAP for the overall study sample and for the age subgroups, with a significant effect only in subjects aged 65 years or more, with an OR that remained almost invariable after adjusting by age and sex. In the study sample passive smoking exposure at home was not associated with other known risk factors for CAP,

such as chronic bronchitis, COPD, upper respiratory tract infection in the previous month, hospital admission in the previous 5 years, history of any previously confirmed pneumonia, sudden changes of temperature in the workplace in the previous 3 months, so that passive tobacco consumption was not adjusted by these variables.

The annual incidence of CAP in subjects exposed and non-exposed to passive smoking in home environment, Risk Ratio (RR), Attributable Risk (AR), and Etiologic Fraction (EF) for the overall study sample and for subgroups of age is summarized in Table 2. A statistically significant effect of passive tobacco exposure was observed in subjects aged 65 years or older; in which passive smoking carry a 48% increase in the risk for CAP.

Discussion

The results of the present analysis show that age modify the effect of passive smoking on CAP. In 65 year subjects or older passive smokers are at higher risk for CAP than non-exposed subjects, with an OR of 1.59, while this effect disappeared in subjects under 65 years of age. There is abundant scientific evidence on the effect of tobacco on CAP but evidence on the effect of passive smoking is scarcer. It is well known that smoking is one of the main independent risk factor for CAP and determines its severity. [7,16-18] This risk is directly associated with the number of cigarettes smoked and it is reduced after quitting.[8] Probably this may be explained by structural pulmonary lesions and alterations of the immune response, both innate and adaptative, as a result of smoking [19,20] which may favour the presence and propagation of microorganisms in the bronchial tree. Also, tobacco consumption increases tissue oxidative stress especially in the lung provoking lesions in the respiratory epithelium, connective tissue and vascular endothelium, which may increase their sensitivity to the inflammatory

aggression of the infection,[19-21] even at low concentrations of smoke.[22] For these profuse mechanisms, tobacco smoke may be an important risk factor for CAP also in passive smokers.[9,10]

The effect of passive smoking on the risk of CAP has been previously reported in patients older than 65 years requiring in-patient care for CAP [12] and in patients with pneumococcal bacteremia between 18 and 64 years of age.[11] However, the influence of passive smoking exposure on the appearance of CAP in adults of all ages on the basis of a population-based study was not well-known and uncertain. Nuorti JP et al.[11] showed that smoking was the main independent risk factor for invasive pneumococcal disease in immunocompetent adults aged between 18 and 64 years, with an OR of 4.1 in active smokers and 2.5 in passive smokers. In the present study, exposure to passive smoking at the home environment only showed an effect in subjects 65 years or over, in which a 59% risk excess was observed. Age seems to modify the effect of passive smoking on CAP but it is not clear if this interaction is due to age "per se" or if it is due to a more prolonged exposure or a different exposure pattern or intensity to passive tobacco smoke at home in elderly subjects. Moreover, in older persons the defense mechanisms may be more impaired and outweighed by this aggression. By contrast, in younger subjects, specific and nonspecific defense mechanisms may counterbalance the aggression of tobacco smoke provoked by other smokers.

The prevalence of passive smokers at home observed in the present study is very similar to those previously published regarding Spanish population in 2005 (29.5%), previously to entering into force the smoking ban,[23] which reinforce the reliability of the present data. This prevalence indicates the magnitude of the exposure to a factor which has a remarkable impact on the risk of CAP. Thus, approximately one third of

pneumonic episodes in passive smokers >65 years of age are due to exposure to tobacco smoke from other persons at home and could be avoided if this factor was eliminated. The present findings, together with the evidence of the effectiveness of pneumococcal vaccine [24,25], in particular, the conjugate vaccine,[26] suggest that vaccination could be administered not only to active smokers, but also to subjects older than 65 years of age who cannot quit to be exposed to passive smoking in the household environment. The main study limitation include the inaccuracy for quantitative measuring passive tobacco smoke exposure since, for example, exposure intensity was not considered and co-inhabitats who smoke at home may go to smoke outside. However, this circumstance was the same for cases and controls and, although it may have diluted the expected effect, a bias was not introduced. We have not taken into account passive exposure at work or in public places, which are now forbidden but were allowed when the study was conducted, because our aim was focused on the effect of passive smoking at home.

In summary, the present study adds new evidence on the effect of passive smoking on CAP in adults from a population-based study. It shows a significant effect only in subjects 65 years old or over, who may be exposed for a more prolonged period of time, with a more intensive pattern of exposure and whose pulmonary defense mechanisms may be impaired or debilitated. These results must be taken into account when considering preventive measures for CAP in this specific age population, such as changes in life style factors or vaccination.

Support statement

Fondo de Investigaciones Sanitarias (FIS 99 / 0002-01) and CIBER de Respiratorio 06/06/0028 Madrid, Spain.

Conficts of interest statement

None to be declared

Authors' contributions to the study

JA, MSP, IB and AT have designed the study, contributed in the field work and write the manuscript

EP has performed the statistical analysis

JR, IH, EC, MA, PA and AE contributed in the field work

JA is the guarantor of the study.

Acknowledgements

The authors thank Marta Pulido, MD, for editing the manuscript and editorial assistance. The fees of medical editing were supported by Fundació Privada Salut del Consorci Sanitari del Maresme.

References

1. Torres A, Blasi F, Peetermans WE et al. The aetiology and antibiotic management of community-acquired pneumonia in adults in Europe: a literature review. *Eur J Clin Microbiol Infect Dis* 2014; DOI 10.1007/s10096-014-2067-1

2. Torres A, Peetermans WE, Viegi G, et al. Risk factors for community-acquired pneumonia in adults in Europe: a literature review. *Thorax* 2013; 68: 1057-1065

3. Oseasohn R, Skipper BE, Tempest B. Pneumonia in a Navajo community: a two-year experience. *Am Rev Respir Dis* 1978; 117: 1003-1009

4.Gil-Prieto R, García-García L, Álvaro-Meca A, et al. The burden of hospitalisations for community-acquired pneumonia (CAP) and pneumococcal pneumonia in adults in Spain (2003–2007). *Vaccine* 2011;29:412-416.

5.Arcavi L, Benowitz NL. Cigarette smoking and infection. *Arch Intern Med* 2004; 164: 2206-2216.

6. Hoffman LH, Strutton DR, Stang PE, et al. Impact of smoking on respiratory illness-related outpatient visits among 50-to 75-year-old in the United States. *Clin Ther* 2002;24:317-324.

7. Almirall J, Bolíbar I, X. Balanzó X, et al. Risk factors for community-acquired pneumonia in adults: a population-based case control study. *Eur Respir J* 1999;13:349-355.

8. Almirall J, González CA, Balanzó X, et al. Proportion of community-acquired pneumonia cases attributable to tobacco smoking. *Chest* 1999;116:375-379.

9. Vinogradova Y, Hippisley-Cox J, Coupland C. Identification of new risk factors for pneumonia: population-based case-control study. *Br J Gen Pract* 2009;59:e882-e887.

10. Jones LL, Hashim A, McKeever T, et al. Parental and household smoking and the increased risk of bronchitis, bronchiolitis and other lower respiratory infections in

infancy: systematic review and meta-analysis. *Respir Res* 2011;12:5, doi: 10.1186/1465-9921-12-5.

11. Nuorti JP, Butler JC, Farley MM, et al. Active bacterial core surveillance team. Cigarette smoking and invasive pneumococcal disease. *N Engl J Med* 2000;342:681-689.

12. Loeb M, Neupane B, Walter SD, et al. Environmental risk factors for community-acquired pneumonia hospitalization in older adults. *J Am Geriatr Soc* 2009;57:1036-1040.

13.Jiménez-Ruiz CA, Miranda JA, Hurt RD, et al. Study of the impact of laws regulating tobacco consumption on the prevalence of passive smoking in Spain. *Eur J Public Health* 2008;18:622-625.

14. Almirall J, Bolibar I, Serra-Prat M, et al. Community-Acquired Pneumonia in Catalan Countries (PACAP) Study Group. New evidence of risk factors for community-acquired pneumonia: a population-based study. *Eur Resp J* 2008;31:1274-1284.

15.http://www20.gencat.cat/docs/salut/Home/El%20Departament/Estadistiques%20sanitaries/Enquestes/02_enquesta_catalunya_continua/Documents/Arxius/informeesca2012.pdf

16. Pastor P, Medley F, Murphy TV. Invasive pneumococcal disease in Dallas County, Texas: results from population-based surveillance in 1995. *Clin Infect Dis* 1998;26:590-595.

17. Garcia-Vidal C, Ardanuy C, Tubau F, et al. Pneumococcal pneumonia presenting with septic shock: host- and pathogen-related factors and outcomes. *Thorax* 2010;65:77-81.

18. Marrie TJ, Shariatzadeh MR. Community-acquired pneumonia requiring admission to an intensive care unit: a descriptive study. *Medicine (Baltimore)* 2007;86:103-111.

19. Hodge S, Hodge GI, Ahern J, et al. Smoking alters alveolar macrophage recognition and phagocytic ability. *Am J Respir Cell Mol Biol* 2007;37:748-755.

20. Huttunen R, Heikkinen T, Syrjänen J. Smoking and the outcome of infection. *J Intern Med* 2011;269:258-269.

21. Arnson Y, Shoenfeld Y, Amital H. Effects of tobacco smoke on immunity, inflammation and autoimmunity. *J Autoimmun* 2010;34:J258-J265.

22. Strulovici-Barel Y, Omberg L, O'Mahony M, et al. Threshold of biologic responses of the small airway epithelium to low levels of tobacco smoke *Am J Respir Crit Care Med* 2010;182:1524-1532.

23. Jiménez-Ruiz CA, Miranda JAR, Hurt RD, et al. Study of the impact of laws regulating tobacco consumption on the prevalence of passive smoking in Spain. Eur J Public Health 2008;18:622-625.

24. Pearson WS, Dube SR, Ford ES, et al. Influenza and pneumococcal vaccination rates among smokers: data from the 2006. Behavioral Risk Factor Surveillance System. *Prev Med* 2009;48:180-183.

25. Centers for Disease Control and Prevention. Recommended adult immunization schedule. United States. 2011 Proposed Revisions. Advisory Committee on Immunization Practices. October 28, 2010

26. De Roux A, Schmöele-Thoma TR, Siber GR, et al. Comparison of pneumococcal conjugate polysaccharide and free polysaccharide vaccines in elderly adults : conjugate vaccine elicits improved antibacterial immune responses and immunological memory. *Clin Infect Dis* 2008;46:1015-1023.

Table 1. Effect of passive tobacco consumption at home on the risk of CAP

Passive smoker	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)*
Overall study population	1.22 (0.93-1.61)	1.18 (0.90-1.57)
Subjects < 65 years	1.02 (0.71-1.46)	0.98 (0.68-1.41)
Subjects ≥ 65 years	1.59 (1.02-2.48)	1.56 (1.00-2.45)

*Effect adjusted by age and sex.

Table 2. Incidence of CAP and the impact of exposure to passive smoking at home

Never smokers	Annual incidence of CAP	Relative risk (95% CI)	Attributable risk (95% CI)	Etiologic fraction %
Overall study population				
Passive smokers	$1.14/10^3$ inhabitants	1.26 (1.02-1.55)	$0.235/10^3$ inhabitants (0.234-0.235)	20.6
Non-passive smokers	$0.90/10^3$ inhabitants			
Subjects aged < 65 years				
Passive smokers	$0.75/10^3$ inhabitants	1.14 (0.87-1.51)	$0.094/10^3$ inhabitants (0.094-0.095)	12.5
Non-passive smokers	$0.66/10^3$ inhabitants			
Subjects aged ≥ 65 years				
Passive smokers	$2.50/10^3$ inhabitants	1.48 (1.08-2.03)	$0.811/10^3$ inhabitants (0.810-0.812)	32.5
Non-passive smokers	$1.69/10^3$ inhabitants			

CAP: Community acquired pneumonia. CI: confidence interval.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract YES (see page 3: abstract)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found YES (see structured abstract in page 3)
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Yes (page 4)
Objectives	3	State specific objectives, including any prespecified hypotheses Yes (page 4)
Methods		
Study design	4	Present key elements of study design early in the paper: YES (page 4)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection: YES (page 5-6)
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up NO *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls: **YES** (page 5-6) *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants: No
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case: YES (page 5)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable: YES (page 5-6)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group: YES (page 5)
Bias	9	Describe any efforts to address potential sources of bias: YES (page 5)
Study size	10	Explain how the study size was arrived at: YES (page 5)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why: YES (page 6-7)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding: YES (page 6-7)
		(*b*) Describe any methods used to examine subgroups and interactions: YES (pages 6-7)
		(*c*) Explain how missing data were addressed: YES (pages 6-7)
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed: YES (page 5) *Cross-sectional study*—If applicable, describe analytical methods taking account of

	sampling strategy
	(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. YES (page 7)
		(b) Give reasons for non-participation at each stage YES (page 5)
		(c) Consider use of a flow diagram. NO
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. No (previously published)
		(b) Indicate number of participants with missing data for each variable of interest. YES (page 7)
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure YES (page 7-8, and tables 1 and 2)
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included. YES (page 7-8)
		(*b*) Report category boundaries when continuous variables were categorized. YES (see page 7-8)
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period. YES (see table 2)
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses. YES (page 7-8)
Discussion		
Key results	18	Summarise key results with reference to study objectives YES (page 8)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias. No
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. YES (page 8-10)
Generalisability	21	Discuss the generalisability (external validity) of the study results. YES (page 8-10)
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based. YES (page 11)

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.